Early Predictors of Transfusion and Mortality After Injury: A Review of the Data-Based Literature

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Trauma is the leading cause of mortality in the first four decades of life and even though later superseded by heart disease and malignancy, remains a significant cause of death and disability among all age groups. In all settings, hemorrhage is one of the most substantial determinants of poor outcomes and death.[1,2] Though blood transfusion has the obvious benefit of volume restoration and improved oxygen carrying capacity in the injured patient, there are risks and consequences to the use of blood including transfusion reaction, transmission of blood-borne pathogens, and impact on limited supply. In the past several years, evidence has emerged that allogeneic red blood cell transfusion may have significant deleterious immunologic impact upon the injured host.[3–6] For all of these reasons, there has been a trend to restrict transfusion in non-urgent clinical settings, and, in general, replacement of blood loss is reserved for urgent conditions in which patients exhibit signs and symptoms of class III or class IV hemorrhage, that is, ongoing or imminently life-threatening. Through this same period, knowledge of the cellular mechanisms of shock and the physiologic response to resuscitation has increased greatly and could be anticipated to provide data-based guidance for changes in practice. The purpose of this paper is to review published data sets on early indicators of mortality after trauma and for the need for transfusion and then, based on these data, to evaluate the risk/benefit ratio of contemporary transfusion strategies in these injured patients.

METHODS/SEARCH STRATEGY

To develop this review, a systematic search of available scientific evidence was conducted utilizing OVID/MEDLINE (1966–present). Selected search terms included combinations of the flowing key words and terms: "trauma", "injury", "blood", "transfusion", "hemorrhage", "mortality", "outcome", "base deficit", "coagulopathy", "hypothermia", "physiology", "blood pressure" and "SIRS". Accessory searches were also conducted using the Cochrane Database of Systematic Reviews 2005 (http://www.cochrane.org), the National Guideline Clearinghouse (http://www.guidelines.gov/index.asp), and the Agency for Healthcare Research and Quality (AHRQ) (http://www.ahrq.gov). In addition, reference lists and bibliographies were analyzed for additional relevant articles.

Prediction of Blood Transfusion After Injury

The National Blood Data Resources Center report of 2002 states that approximately 12,000,000 units of packed red blood cells (pRBC) are transfused each year in the United States and that ten to fifteen percent of the national blood supply is directed toward the treatment of injured patients.[7] Como and his colleagues reviewed one year's admissions to the Shock Trauma unit at the University of Maryland Medical Center. Of the 5645 patients admitted, eight percent were transfused. Four hundred seventy nine (479) received 5,219 units of pRBC. Overall mortality in the transfused group was 27%. The 3% of the total population who received more than ten units of blood had a mortality of 39%.[8] It is unclear from these data to what degree transfusion itself contributed independently to this increase in mortality. Similar findings have been demonstrated by Dunne et al.[9]

Since substantial numbers and proportions of injured patients receive red blood cell (RBC) transfusion, it is important to know who actually needs this intervention. Evaluation of the literature suggests several important predictors of the need for RBC transfusion. These include specific parameters of pre-hospital and presentation physiology, assembled as trauma scoring systems, and additional physiologic parameters during resuscitation, including measures of oxygen debt, injury severity, coagulopathy, and hypothermia.

Scoring Systems

Numerous physiologic scoring systems have been developed over the two decades for the initial evaluation of the trauma patient. These include pre-hospital index, trauma score, and revised trauma score. All of the scoring systems

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currently in use include blood pressure, respiratory rate, and Glasgow Coma Score. In a small review of 250 patients, published in 1983, West and colleagues compared age, sex, injury severity, mechanism of injury and trauma score. Their results suggested that trauma score was the best predictor of blood requirement among those predictors evaluated. Of the patients with trauma scores <14, 90% did not require transfusion, whereas, 70% of patients with trauma scores ≥14 did required transfusion.[10] Similarly, Jones demonstrated, in a study population of 217 patients, that a pre-hospital index score >3 was associated with a 77% chance of requiring red cell therapy and, among those with a pre-hospital index score ≤3, only 14% required transfusion.[11] In a series published in 2002 by Starr and colleagues, the revised trauma score showed a significant correlation with the requirement for blood transfusion after traumatic injury and pelvic fracture.[12] Given the complexity of some of the pre-hospital trauma scoring systems, Franklin and colleagues evaluated pre-hospital hypotension as a surrogate for pre-hospital scoring and found that nearly 50% of patients with survivable pre-hospital hypotension required specific therapy for hemorrhage.[13]

Injury severity scoring has been demonstrated to correlate with transfusion volume. In Como's study, survivors had an associated trend toward increased transfusion with increasing ISS. Patients requiring 1–10 units of pRBC had a mean ISS of 17, patients requiring 11–20 units had a mean ISS of 28, and those requiring >20 units had a mean ISS of approximately 33.[8] In Malone's cohort of 15,534 trauma patients, a mean ISS 22 was associated with transfusion, whereas a mean ISS of 8 was not. In as yet unpublished data from combat casualty care in the current conflict in Iraq, Eastridge, Wade and Holcomb show similar results, that is, that there is a positive correlation between increasing injury severity score and increasing likelihood of transfusion.

Combinations of physiologic scoring data and injury severity have also been used to attempt to predict the need for transfusion. Baker and colleagues identified 4 risk factors for transfusion after injury: blood pressure <90 mm Hg, heart rate >120, GCS <9, and high risk injury (trauma to the central chest, abdominal injury with diffuse tenderness, survival of a vehicular crash in which another occupant died, vehicular ejection, or penetrating torso injury). Patients with all 4 risk factors had a 100% transfusion rate; 3/4 factors, 68%; 2/4 factors, 42%; 1/4 factors, 12%, and 0/4 factors, 2%. In this series, blood pressure <90 mm Hg demonstrated the highest relative risk for transfusion.[18]

Oxygen Debt

Perhaps the most convincing data on early predictors for blood transfusion is in the compendium of scientific literature on oxygen debt. Davis and colleagues evaluated 192 trauma patients with shock—defined by base deficit after injury—and correlated these findings with blood transfusion data. Base deficits 2–5 were associated with blood transfusion requirements of 213 mL, 311 mL and 401 mL at 1, 2 and 24 hours respectively. Base deficits 6–14 were associated with blood requirements of 583 mL, 1,201 mL, and 1,538 mL at corresponding time points, and base deficits >15 were associated with 1,082 mL, 2,097 mL, and 2,476 mL, respectively.[14] In a later study, Davis, Parks et al., substantiated the dose-dependent response between admission base deficit and volume of transfusion, demonstrating that in this second group of patients, those with a base deficit 3–5 required 1.4 units of pRBC, base deficit 6–9 required 3.8 units of pRBC, and >10 required 8.3 units of pRBC at 24 hours post admission. Interestingly, these oxygen debt data also correlated in a stepwise fashion with diminished trauma score and revised trauma score.[15] Serum lactate has also been used as a marker of tissue oxygen debt, with similar results.[16,17]

Coagulopathy and Hypothermia

Coagulopathy and hypothermia have also been used to predict the need for transfusion, however, they are not mutually exclusive, and their interactions are complex and further complicated in any given individual by the nature and degree of injury. Acute traumatic hemorrhage, resuscitation, and transfusion are all independently associated with abnormalities of clotting factors, acid-base homeostasis, and thermoregulation. Coagulation in the injured patient is disrupted by consumption and dilution of coagulation factors, hypothermia, acidosis, excessive fibrinolytic activity, and tissue thromboplastin released in response to brain and other tissue injury. Thrombo-elastography is useful in the evaluation of platelet dysfunction and fibrinolysis and appears also to have some utility in predicting the necessity for blood transfusion in injured patients.[19,20]

Jurkovich was one of the first investigators to evaluate the effects of hypothermia after injury, demonstrating substantially decreased survival with progressively worsening hypothermia.[21] Numerous investigators have carried this work forward, correlating hypothermia with blood loss and the necessity for red cell transfusion.[22–25] Luna and colleagues have shown that blood transfusion requirements are directly proportional to injury severity and inversely proportional to core temperature. The degree to which transfusion itself may be causally related to decreasing temperature was not clear from this study but must be considered. Ferrara and colleagues, in a study of operative trauma patients at the Detroit Receiving Hospital, compared blood loss between those patients with intra-operative core temperatures between 33–35 degrees and those with core temperature >35 degrees centigrade (°C). Intra-operative blood loss averaged 540 mL in those maintaining core temperature >35°C and 1820 mL, in the profoundly hypothermic group (33–35°C), a greater than three-fold difference. Unfortunately, blood transfusion requirements in the study groups is not reported.[24] Whatever their limits as observational data sets, these results imply close correlation between hypothermia and coagulopathy in trauma and the likelihood of the need for transfusion.

Prediction of Mortality After Injury

A number of variables predicting the likelihood of mortality after injury have been reported in the medical literature. In this review, we concentrate on early predictive indices and, specifically, on those related to blood transfusion. Not surprisingly, many of the same factors that predict RBC transfusion also predict patient mortality. These include pre-hospital and presentation physiology, measures of oxygen debt, injury severity, coagulopathy and hypothermia, and evidence of systemic inflammatory response syndrome on admission.

Scoring Systems

A large prospective cohort study of over 20,000 patients by MacLeod and colleagues in Florida demonstrated a number of factors associated with mortality in injured patients. The most significantly predictive included partial thromboplastin time (PTT), abnormal computerized tomography (CT) of the head, low initial hemoglobin, a base deficit, and hypotension in the emergency department.[26] Trauma scoring systems for use in the field or upon presentation to the emergency department have only a moderate predictive capacity to determine mortality after injury.[27–30] Kuhls and colleagues studied a multivariable model strategy in which physiologic trauma score (admission SIRS score—see below—Glasgow Coma score, and age) provided superior predictive potential when compared with anatomic scoring systems such as injury severity score.[28] In a related study, Bochicchio demonstrated that SIRS score (temperature >38°C or <36°C, heart rate >120 beats per minute, respiratory rate >20 per minute, leucocytosis >12,000 or <4,000 cells per mL) was an independent predictor of mortality after injury. The relative risk of mortality increased ten-fold from a value of SIRS = 1 (3.5%) to SIRS = 4 (37.3%).[31]

Base Deficit

Numerous investigations have demonstrated an association between elevated base deficit and increase in patient mortality after injury.[14–15,32–36] However, specifically, the failure to resuscitate from oxygen debt within the first 24 hours is correlated with the worst prognosis. Kincaid, Chang and their colleagues showed that patients whose base deficits could not be improved by resuscitation to >4 by 24 hours into care, had a 50% mortality. Those whose base deficit could be normalized within 24 hours had only a 9% risk of mortality.[33] In their study of major trauma patients with occult hypo-perfusion demonstrated by lactic acidosis during the first 24 hours of ICU care, Blow and colleagues showed that of the 44/58 patients whose lactic acidosis could be corrected within the first 24 hours, none died. Among the remaining 14 patients, those with persistent lactic acidosis, 43% died.[34]

Anatomic injury severity demonstrates a modest statistical relationship with adverse survival outcomes after injury.[37–38] Age shows strong positive correlation with mortality after injury, out of proportion to that which can be explained by simple anatomic scoring algorithms.[39–40]

Hypothemia

In several of the series cited above, increasing hypothermia is correlated with increasing mortality. Temperature of <34°C is associated with 40–60% patient mortality,[22–24] and this association becomes stronger with decreasing core temperature.[21] Patients with significant hypothermia in these studies were also prone to coagulopathy. In the study by MacCleod et al., abnormal protime (PT) and partial thromboplastin time (PTT) were independent risk factors for mortality after trauma.[25]

Transfusion as a Predictor of Mortality

A substantial medical literature links increasing volume of blood transfusion after injury with increased mortality.[3,41–60] Due the heterogeneity of the patient populations involved and the pathophysiology of severe trauma, elucidating the true relationship between blood transfusion and mortality in the severely injured patient has been difficult. However, concern has arisen recently that allogeneic blood therapy has a more than just statistically independent association with mortality in trauma patients.[3,43,48] Robinson evaluated blood transfusion in a sample population of blunt hepatic and splenic injuries. Mortality in this population was 14.2%. Utilizing multiple logistic regression analysis and controlling for indices of shock and injury severity, blood transfusion was a strong predictor of mortality, with an odds ratio of 4.75. This result was even more substantial in patients managed non-operatively: transfused patients were 8.45 times more likely to die from their injury than those who were not transfused.[43] Red blood cell transfusion and patient age were both found to be independently associated with increased patient mortality from all causes of injury, and these two markers also acted synergistically, to predict mortality from all causes of injury.[48] Malone and colleagues, as noted above, evaluated a cohort of 15,534 trauma patients of whom 1,703 required blood transfusion. In this cohort, transfused patients were older, had higher injury severity scores, lower GCS scores, more significant tissue oxygen debt, and were more likely to have a penetrating mechanism of injury. However, statistical analysis identified blood transfusion as the strongest independent predictor of death in these patients.[3]

CONCLUSIONS

Despite the limitation that many of the analyses in this review were done on class II and class III data, that is, data from retrospective, observational studies, it is apparent that the need for blood transfusion in trauma patients can be predicted by variables measured early in the patient's resuscitative course. These include: prehospital and presentation physiology, measures of oxygen debt, injury severity, coagulopathy, and hypothermia. Shock indices and measures of oxygen debt appear to be strong positive predictors of transfusion volume requirements and transfusion volume require-

ments, in turn, appear to be strong predictors of mortality in this patient group.

Future areas for research in this area will be studies aimed at further quantifying these variables to more accurately predict transfusion volume needs. Additional important areas of research include optimal timing of blood transfusion, so-called "transfusion triggers", and the effects and outcomes of massive transfusions.

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DISCUSSION

Dr. Donat Spahn: I think you have convinced me that the more severely you are injured, the more likely you are to receive a blood transfusion, the more likely you go into multi-organ failure and the more likely you are going to die. But what is the contribution of each of these different factors? I think we have no answer. Is it interrelated, or can we dissect the effects of each different factor? Is it really transfusion that leads to the complication and death, or is it simply the fact that those who received the transfusion are more severely injured in the first place? For a more controlled situation of surgery or intensive care unit, there's only one study that has ever approached this, the TRICC trial. A subgroup analysis published earlier this year, only 200 patients, found no difference. In terms of outcome, there were very slight trends of less infection and less multi-organ failure in the lesser transfused group, but nothing real. On the other hand, the study wasn't powered nor designed to have the power to answer these questions. So my question is can we avoid a prospective randomized study in this patient group, at least in the civilian arena, to answer this question? If we conduct a study, I propose that we have strict guidelines, not only for red blood cells, but for all the blood components as well. And, of course, the problem is what type of blood product and what type of red blood cells do we use?

Dr. Stephen Cohn: Over the last decade a number of folks in the room here have been trying to design clinical trials that address transfusion avoidance. How do we design a trial that will allow us to discern a reduction in transfusion requirements? This kind of work aims at trying to identify the at-risk group for transfusion requirements to define our study group. In some ways, we're in need of technology. Imagine that your soldiers wore monitors that could measure base deficit real time continuously and transmit it to an AWAC, or to Dr. Holcomb at the ISR who could say, this guy needs to go to the Combat Support Hospital not to the Battalion Aid Station because he's going to bleed to death. We're not quite there yet. But even if this information would be very valuable in terms of trial design, I'm not sure as clinicians how much it would change our management because in most situations we're already in the mode of transfusing someone even before we get base deficits back.

Dr. Lloyd Ketchum: As we try to design rational clinical trials of massive transfusion, that we're talking about a very small subset of patients. Can we come up with a way to predict in the trauma bay with very readily available data which person is going to require massive transfusion and which person is not?

Dr. Brian Eastridge: This will not guide anybody's specific therapy. But, as was mentioned by the discussants, this was more of a baseline to figure out who are those specifically at risk for massive transfusion.

Dr. Debra Malone: Is it blood transfusion or is it shock, injury severity, base deficit or everything else that goes into it? To the best of our ability, statistically, we really think we have determined that blood transfusion in and of itself, after controlling for indices of shock and patient demographics, is an independent predictor of worse outcome.

The big picture here is how do we develop a prospective clinical trial? That's going to be tough, because I think we're talking about two different things. We're talking about systemic inflammation and what goes bad because of systemic inflam-

mation. There is this other entity though, massive transfusion. Until we actually have a better way to replace blood volume, I don't know that it's going to be possible to develop a prospective randomized clinical trial for blood transfusion.

Dr. John Owings: Is blood transfusion fundamentally bad? The answer is yes and no. We're looking at some fairly esoteric immunologic consequences of transfusion, including leukocyte survival in trauma patients, which is unique in the trauma population compared to other populations. If you give it when you don't need it, then that's obviously bad, because transfusion has very, very poor consequences. If you don't give enough that's a problem. So ideally why we're all here is to try to figure out a way to minimize the need for transfusion so that we hit right squarely in the center zone, which is only transfuse absolutely the minimum amount. The point the presenter made is that, when we swing too far in either direction, the cure then becomes worse than the disease.

Dr. Morris Blajchman: But the allogeneic RBCs that we use to replace bleeding is not the best product, the blood that we use to replace stored blood is acidotic and hyperkalemic due to storage. In addition, stored RBCs have storage defects, which render the RBCs hypofunctional. Mortality occurs primarily when the hemoglobin is below six grams per dL. So we know that it is unnecessary to get patients back to 10 or 12 g/dL or even 10 g/dL, which often happens in patients because they are over-transfused. My main message is that we don't have to replace the hemoglobin to physiologically "normal" levels. Just because we're all walking around with hemoglobin levels of 15 g/dL doesn't mean that that's the best level to achieve when transfusing trauma patients.

Dr. Spahn: I completely agree. And, you know, the question of what type of blood we're using in such a trial is a key question. Jean-Louis Vincent in the ABC study found there is an add-on negative effect of being transfused in ICU patients. He repeated the same study, exactly the same thing, two years later with leukoreduced blood and they didn't find this anymore. This has not been published yet.

Dr. Jeff Lawson: Our expectation is trauma is chaos. So in that context I think there's some hope. But the analysis is not the conventional analysis that we're all used to. I think the solution will come from the statistical analyses that have been derived from our gene chip array-based information. It's a completely different statistical paradigm and it takes a big sample number.

Dr. John Holcomb: Many studies being designed, or in process right now, are focusing on the critical small segment of trauma patients who need a lot done to them and who might survive. The challenge is to be able to determine the group that will get a fair amount of blood very soon upon arrival in the ED and have the potential of survival. We need to be able to randomize them and not have excessive noise. I think we need to spend more time with these kinds of data. We need to know which parameters we can easily measure in the first ten minutes in the ED, randomize and apply whatever hemostatic intervention we are studying. The next challenge will be using the same construct and moving to the prehospital arena.